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A NEUROPATHOLOGICAL STUDY OF CANCER GROWN IN THE TONGUE AND THE RECTUM

by

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Content

1. INTRODUCTION

The tongue has the most abundant nerve supply of all the viscera. Sensory endings, such as glomerular bodies, sensory corpuscles similar to those of the genital organs, arborized endings and plexiform endings in the tongue have been reported by Prof. SETO, Tohoku University.

As for the sensory apparatus in the rectum WAN WEI FAN of our laboratory reported many afferent nerves with free endings, which were characteristic in having myelin sheaths even near the endings in the mucous membrane and showed secondary degeneration following posterior rhizotomy. On the other hand, JABONERO found sensory endings which showed terminal expansions. The author can find only a few reports on the neuropathological study of tumors. M. ARAKI (1953) detected a fine nerve fiber growing along the blood vessels in YOSHIDA sarcoma which was transplanted into a mouse. He supposed it to be a nerve of the tumor proper. H. YAMADA (1957) of our clinic, who studied the pathologic changes of the nerves in gastric cancer, divided the changes into two kinds. One was the change found in the surrounding or the marginal regions and the other was that within the tumor. He found hyperplasia of the nerve fibers and proliferation of the autonomic terminal networks with partial degeneration in the former, while he observed a dystrophic change of the nerve elements, above all the early disappearance of the autonomic endformations in the latter. V. JABONERO (1957) reported the same results concerning changes in nerve elments in cancer. He supposed that the pathologic change was due mainly to the inflammatory process accompanying the growth of the tumor and not due to the direct action of the tumor cells.

On this problem, YAMADA supposes that the dystrophy of the nerves in tumors occurs because of the pressure of the tumor cells on them.

The author, having much interest neuropathological problems with intimate

relations to pain or other clinical symotoms of tumors, studied the changes in nerves in cancer of the tongue and rectum.

2. MATERIALS AND METHODS

Fresh specimens, taken from the human tongue and rectum, were fixed in 10 % neutral formol solution for 3-4 weeks, and then cut in 30-40 μ with the freezing microtome. Preparation were kept in 10% neutral formol solution again for at least 6 months before staining.

SETO's modification of Bielschowsky's silver impregnating method (SETO's Method) was used for staining the axisclinders and Ehrlich's acid hematoxyline method was used for staining the myelin sheaths.

SETO's Method

The specimens, which have been cut by the freezing method and kept in neutral formol solution, are;

1. Washed with distilled water for a few minutes.
2. Put into 20% silver nitrate solution, being protected from light, for 24-48 hours.
3. Washed in distilled water for 20-30 seconds.
4. Put into 20% neutral formol solution. This solution must be made by diluting the mother neutral formol only with running water, and placed in 4-plates. The specimens are transferred to these plates one by one until the white precipitation disappears.
5. Washed with running water for 30-50 seconds.
6. Placed on filter paper to blot up the water.
7. Immersed in warm ammoniacal silver solution for about 10 minutes.
8. Washed with distilled water twice.
9. Placed in 0.05-0.1% gold chloride solution for 3-4 hours.
10. Placed in 20% sodium thiosulfate solution until the specimens are colored reddish brown.
11. Washed in distilled water.
12. Dehydrated and mounted.

3. CHANGES IN THE NERVES IN CANCER OF THE TONGUE

The neuropathological study was done on two cases of squamous cell cancer or cancroid (Fig. 1).

As stated by YAMADA, the two types of special changes were observed in the marginal region and in the center of tumors.

a) Changes in the marginal zone of the tumor:

The appearance of tumor cells causes the nerve fibers to follow irregular courses (Fig. 2).

The nerve fibers show hyperchromasia and nodular swellings, sometime, with vacuoles like those found in the tissue of chronic inflammation (Fig. 3, 4, 5, 6).

The arborized terminal branches of the nerve fibers, the glomerular sensory

endings and the preterminal networks of autonomic fibers with plasmodia, which were called by STÖHR the "plasma strang" and by JABONERO "nervous syncytium" were observed in the muscular layer extending near the epithelium (Fig. 10, 11).

The fine fibrils in the nervous syncytia changed into granular degeneration in some areas (Fig. 10).

b) Changes in the central region of cancer of the tongue: Hyperchromasia and nodular swellings of the nerve fibers were not observed in the center of cancer. They had almost normal appearances and ran through the cancer tissues, (Fig. 12, 13) which suggested that the nerve fibers are fairly resistant to the infiltration of cancer cells and remain alive though surrounded by them. Sometimes they looked as if they were cut at the margin of a nest of cancer cells (Fig. 16, 17, 18). They are well observed even in the epithelial pearls of cancer (Fig. 19, 20), and in a specimen the author observed an intersting figure of a nerve which alone maintained the connection of an almost demarcated epithelial pearl of cancer to the surrounding tissue (Fig. 21). Myelinated nerve fibers were found in the cancer tissues (Fig. 22, 23). The myelin sheaths appeared almost normal. No nervous syncytium or preterminal reticulum of the autonomic nervous periphery was found in the squamous cancer tissues.

4. CHANGES OF THE NERVES IN CANCER OF THE RECTUM

Neuropathological changes were studied in two cases of adenocarcinoma of the rectum; the preparations stained by the hematoxylin eosin method are shown in Fig. 24, 25. The cancer cells of these two cases invaded from the mucous membrane into the muscle layer. The appearance of cancer cells in the rectum caused a markedly irregular course of the nerve fibers in MEISSNER's plexus first of all. The area of MEISSNER's plexus looked widened. The nerve fibers in the plexus had become loose and markedly winding. However no degenerative changes were observed in the nerve fibers. In the involved lamina propria, the nerve fibers had almost nomal wavy courses (Fig. 28, 29).

In the involved submucous layer, the author could find nerve fibers running almost straight through the cancer cells (Fig. 30, 31). When the cancer cells began to assume the structure of mucous gland, the nerve fibers there went around the cancer cells (Fig. 32, 33, 34), which looked sometime like the water of a rivers tearing clear of a delta (Fig. 35).

In other words, the nerve fibers in an adenomatous cancer, seem to choose their way along the surrounding stroma.

The glandular structure of cancer has a normal appearance in the hematoxylin eosin preparations, but, when impregnated, it presents different features from the normal gland such as the lack of argyrophyle cells.

5. DISCUSSION

The author studied the neuropathologic changes in cancer of the tongue and the rectum. As YAMADA reported, the neurvous changes are divided into two

kinds, changes in the surrounding and in the central area of cancer.

The neural change in the surrounding area is similar to that of chronic inflammations and a characteristic change is found in the center of cancers.

The nerves in the area surrounding a cancer show effects of stimulation such as proliferation of the autonomic terminal networks and hyperplastic sensory fibers together with partial degeneration.

The characteristics of neural change in the center of cancer are as follows.

In cancroid of the tongue nearly normal nerve fibers are found in the cancer tissue. They enter the epithelial pearls without showing marked change. Some of the demarcated pearls are connected with surrounding tissue only by a nerve fiber.

Therefore, the nerve will finally be cut when the pearl falls down. YAMADA described degeneration of the nerve fibers in gastric cancer resulting from the pressure of cancer tissue and some nerve fibers course around the nest of cancer cells to choose their way in the soft stroma.

The author's findings of the nerve fibers in cancroid of the tongue are not identical with his, i. e. the nerve fibers looking almost normal are observable in the midst of the hard cancroid tissue and there is no tendency to detour the cancer tissue. The tongue has many more nerves than the stomach and it consists of mucous membrane and well developed striated muscles.

The mucous membrane adheres tightly to the muscle layer and they are not moved from each other. In the stomach, there is loose connective tissue under the mucous membrane or between the longitudinal and circular muscles.

Therfore, in the stomach the nerve fibers can find space to go around the cancer tissue, while it may be impossible in the tongue. Cancroid of the tongue is a hard cancer and the epithelial pearls consist of horny cells. If degeneration of the nerve fibers in cancer is, as YAMADA described, due to the pressure of cancer tissue, almost all the nerves in cancroid of the tongue should undergo degeneration.

The fact that numerous nerve fibers can be alive in the cancroid tissue stands against YAMADA's opinion.

The author maintains that at least in cancroid the nerve fiber does not show any sign of degeneration due to the pressure of cancer cells.

It is well known that cancer of the tongue is especially painful. Many normal nerve fibers in the cancerous infiltration, some of which are cut and demarcated together with epithelial pearls, may suggest the cause of pain. However, cancroid of the skin is usually painless, though it may involve the tissue with many sensory nerves. Considering this fact the problem of the pain of cancer of the tongue must be studied further.

The appearance of cancer cells in the rectum caused a markedly irregular course of the nerve fibers. As YAMADA described in gastric cancer, some nerve fibers choose their way along the soft stroma. However, a degenerative change of the nerve fibers is not observed. The author found, on the other hand, almost normal nerve fibers running through the cancer tissue in the submucous layer.

Therefore, he is of the opinion that nerve fibers are resistant to some degree against cancer tissue.

The nerve fibers which detour the cell nests of cancer are usally found in adenocarcinoma. When a cancer cells of adenocarcinoma grows between nerve fibers it developes into a glandular structure after repeated cell divisions, and the surrounding tissues are naturally pressed by a cancer cell nest in a radial direction. The author thinks the detouring course of nerve fibers in the adenomatous cancer can be attributed to the special development and arrangement of the cancer cells. If YAMADA's opinion that the pressure of cancer cells is the main cause of nervous degeneration is true, the harder the cancer tissue the heavier will be the destruction of nerve fibers, and cancroid, one of the hardest cancer must be an exception.

6. CONCLUSIONS

(1) The peripheral autonomic nervous structures, such as the preterminal and terminal networks (STÖHR) and nervous syncytium (JABONERO), disappear in the early stage in the growth of cancer tissue.

(2) Nerve fibers of the tongue can enter the epithelial pearls of the cancroid without showing any degenerative change.

(3) Nerve fibers near adenomatous cancer of the rectum detour the cancer tissue and choose their way along the soft stroma.

(4) As JABONERO & YAMADA stated, various stimulatory changes are found in nerve fibers near cancer of the rectum.

(5) As YAMADA detected, the argyrophyl cells were not found in the glandular structure of cancer of the rectum.

(6) YAMADA's opinion that the degeneration of the nerve fibers in cancer is mainly due to pressure by the cancer tissue is not in argeement with the findings in cancroid of the tongue.

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Illustration of figures (Sekiya)

Fig. 1. Cancer of the tongue (Cancroid). Hematoxylin eosin staining × 80

Fig. 2. The same specimen as Fig. 1, stained by Bielschowsky's method. The appearance of tumor cells causes the nerve fibers to follow irregular courses.

Fig. 3. Fig. 4, Fig. 5, & Fie. 6. Nodular swellings of the nerve fibers found in the marginal zone of canceer of the tongue. Bielschowsky's methd × 360

Fig. 7. Peripheral arborization of the nerve fibers in the marginal zone of cancer of the tongue. Bielschowsky's method × 360

Fig. 8. Fig. 9. Special sensory endings found in the marginal zone of cancer of the tongue. Bielschowsky's method × 360

Fig. 10. A preterminal reticulum showing granular change of fibrils in the marginal region of cancer of the tongue. Muscle layer, Bielschowsky's method × 1500.

Fig. 11. Almost normal preterminal reticulum in the marginal region of cancer of the tongue. Muscle layer, Bielschowsky's method × 1500

Fig. 12. Fig. 13 An almost normal nerve fiber running through the infiltration of cancer cells in the tonguue. Bielschowsky's method × 360

Fig. 14. Fig. 15 Nerve fibers running into the cancer cell nests. Cancer of the tongue. Bielschowsky's method × 360

Fig. 16. An almost normal nerve fiber found in the deep part of a cancer cell nest in the tongue. Bielschowsky's method × 360

Fig. 17. Fig. 18, Fig. 19, & Fig. 20. Nerve fibers found in epitheliar pearls of cancer of tongue.

Fig. 21. A nerve fiber which alone maintained the connection of an almost demarcated epitheliar pearl of cancer to the surrounding tissue. Cancer of the tongue. Bielschowsky's method × 360

Fig. 22. A myelinated fiber near an epitheliar pearl of cancer. Cancer of the tongue. Ehrlich's method × 360

Fig. 23. Myelin sheaths near the cancer cell infiltration. Cancer of the tongue. Ehrlich's method × 360

Fig. 24. Cancer of the rectum. Hematoxyline eosin staining × 80

Fig. 25. Another cancer of the rectum. Hematoxyline eosin staining × 80

Fig. 26. A marked irregular course of the nerve fibers in Meissner's plexus. Bielschowsky's method × 360

Fig. 27. High powered photograph of Fig. 26 × 600

Fig. 28. An almost normal nerve fiber found in the involved lamina propria. Belschowsky's method × 320

Fig. 29. High powered photo. of Fig. 28. × 600

Fig. 30. & Fig. 31. Nerve fibers running almost straight through the cancer cells in the involved submucous layer. Bielschowsky's method × 360

Fig. 32, Fig. 33 & Fig. 34 Nerve fibers going around the cancer cells when they begin to assume the structure of mucous glands. Bielschowsky's method × 360

Fig. 35. Nerve fibers looking like the water of a river tearing clear of a delta. Bielschowsky's method × 360

Fig. 36. Lack of argyrophyle cells in the glandular structure of cancer cells. Bielschowsky's method × 360

和文抄録

舌癌及び直腸癌の神経病理学的研究

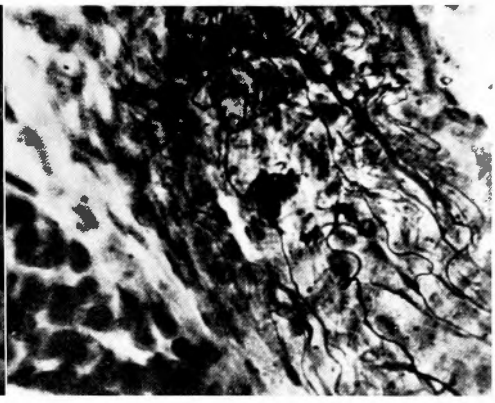
京都大学医学部外科学教室第2講座（指導：青柳安誠教授）

関谷 慎

舌癌及び直腸癌に就いてBielschowsky及びEhrlich法により神経組織の変化を追求した結果，両者共早期に自律神経終網の消失を見たが，終網に到らざる神経繊維は癌組織中にもよく残存し，舌癌では癌真珠の中心に迄明瞭に神経の存在を認めた．直腸の腺癌に於ては癌細胞が中心腔を有する腺状に発育するため，神経組織はその周辺を囲り，恰も癌により圧排されたような形を示すが Cancroid に於てはそのような像はない．

以上の所見から次の結論に達した．即ち神経繊維は癌の圧迫によりて必ずしも変性するものではなく，癌巣に於ける神経の特殊な走行像は癌細胞の特異なる排列と関係があるものであり，癌の神経破壊は終網の如き終末構造から始まるものである．

Fig. 1



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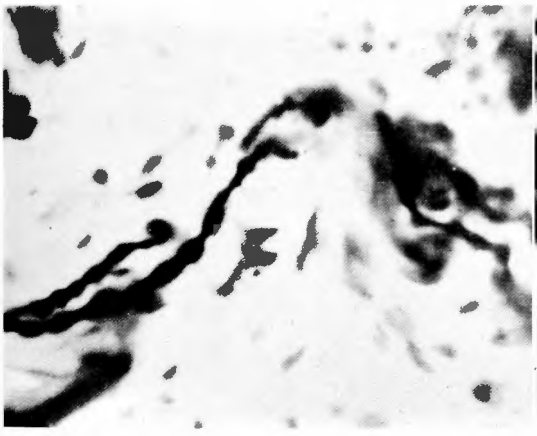

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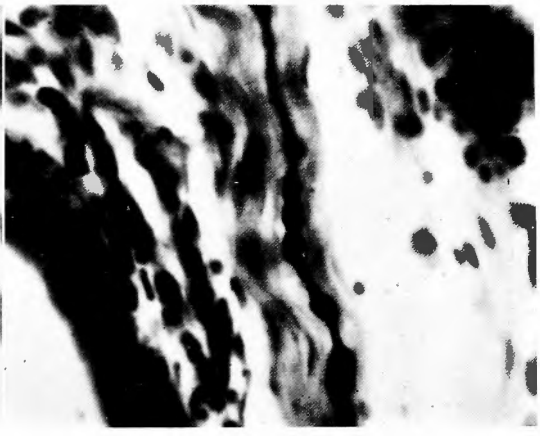

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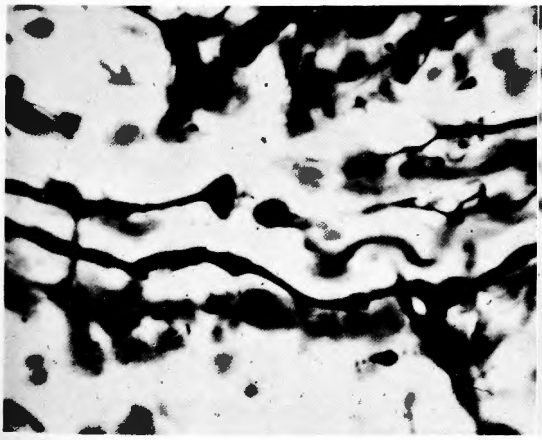

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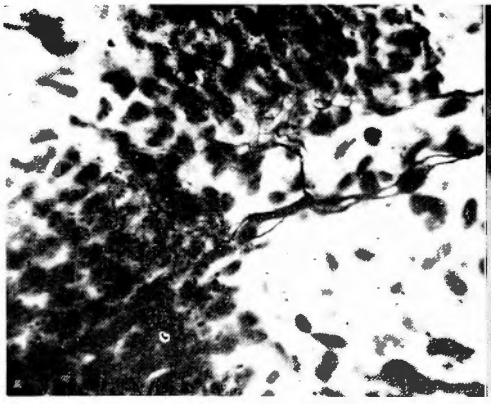

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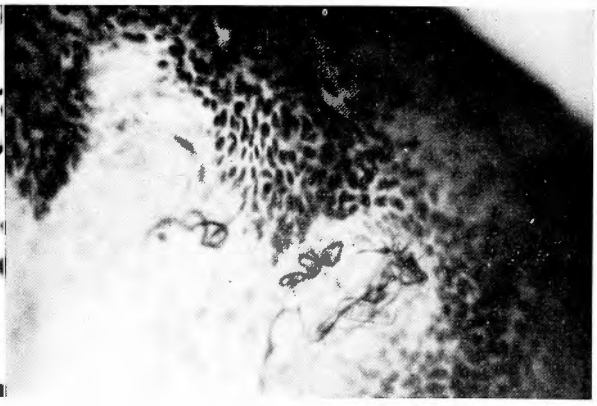

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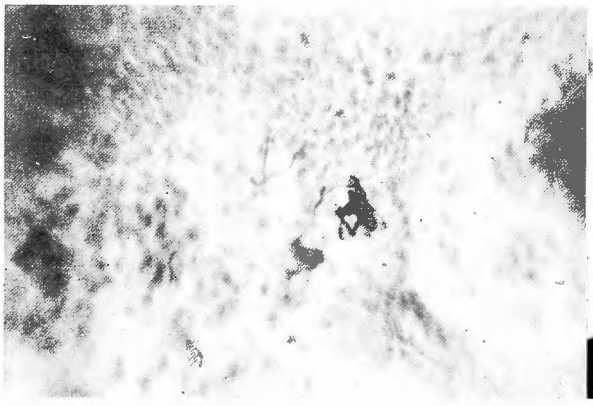
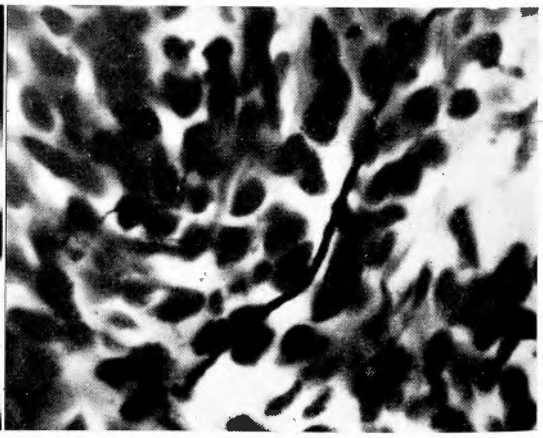


Fig. 9

Fig. 10

Fig. 11



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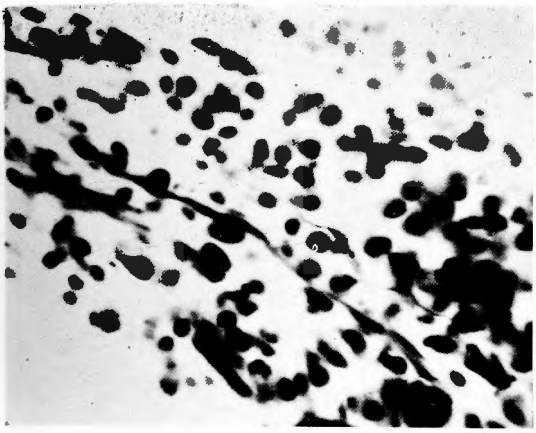

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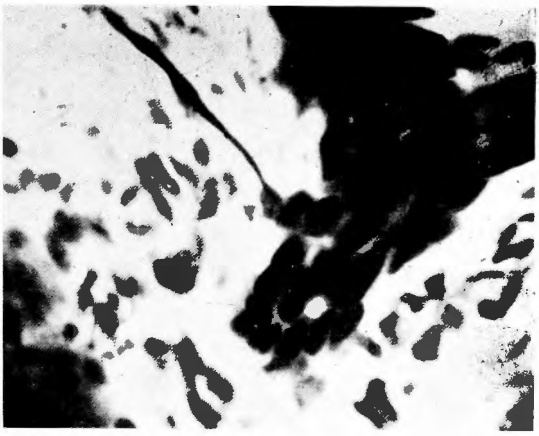

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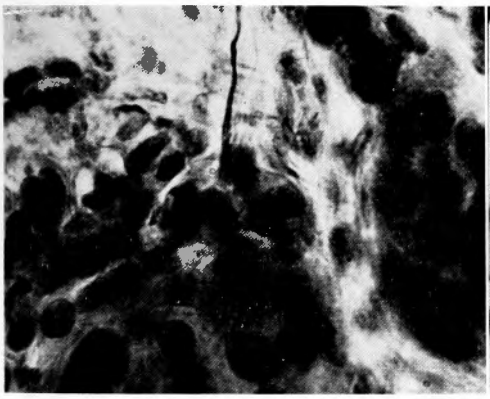

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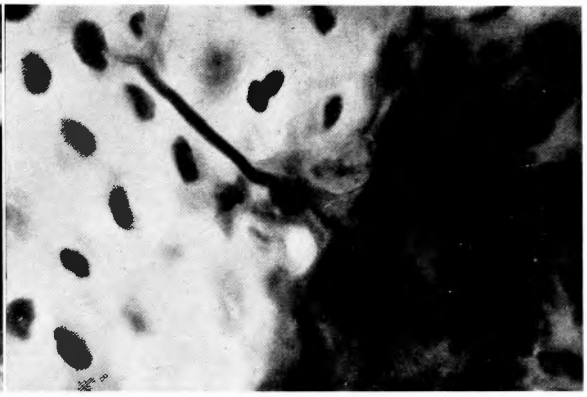

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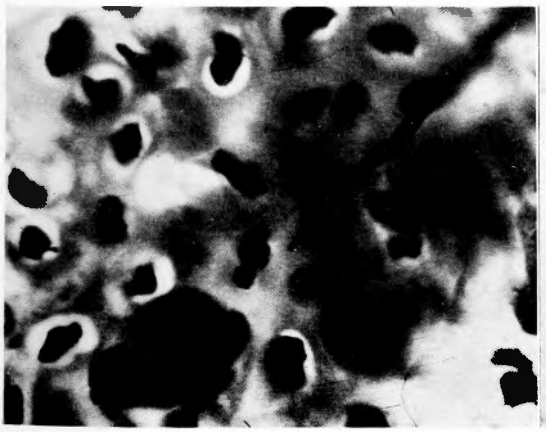

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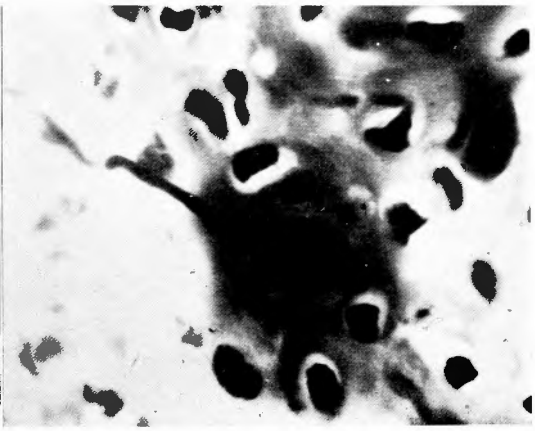

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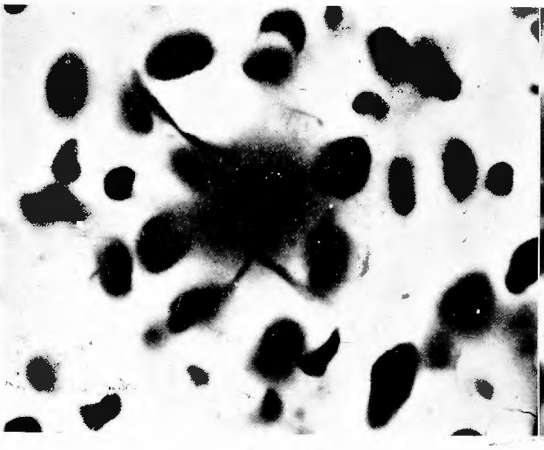

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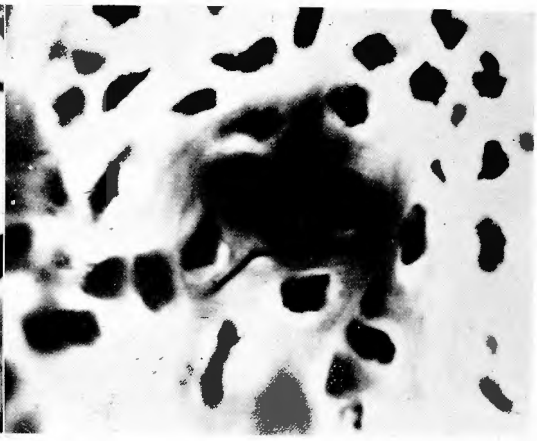

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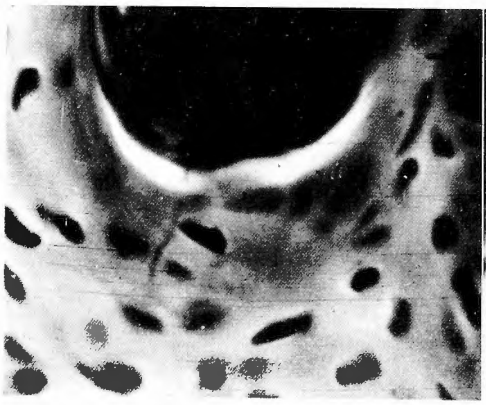

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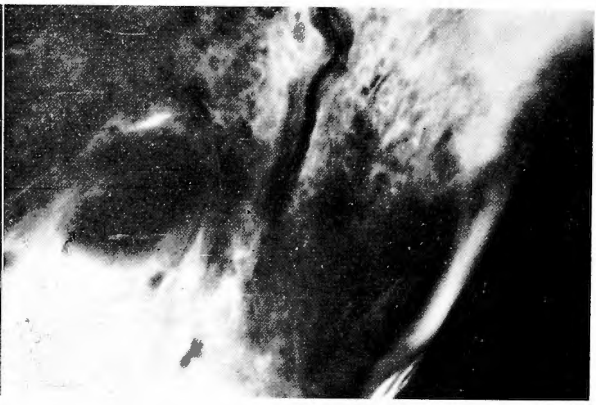

Fig. 22

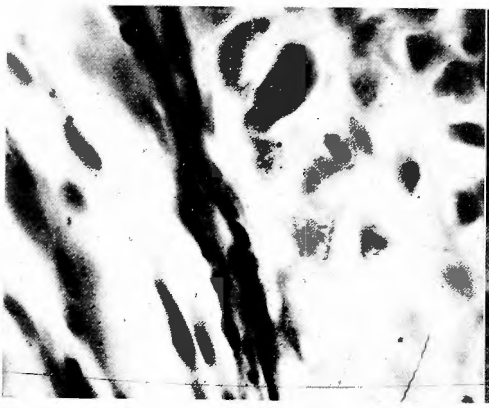

Fig. 23

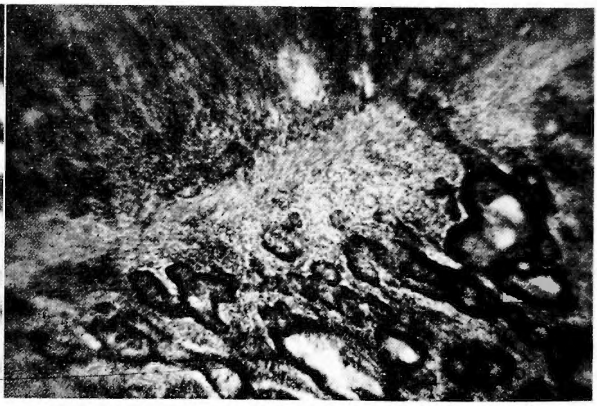

Fig. 24

Fig. 25

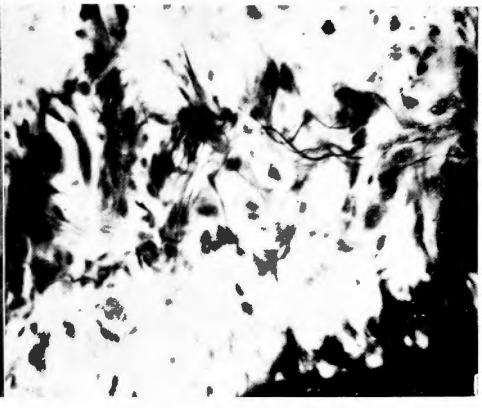

Fig. 26

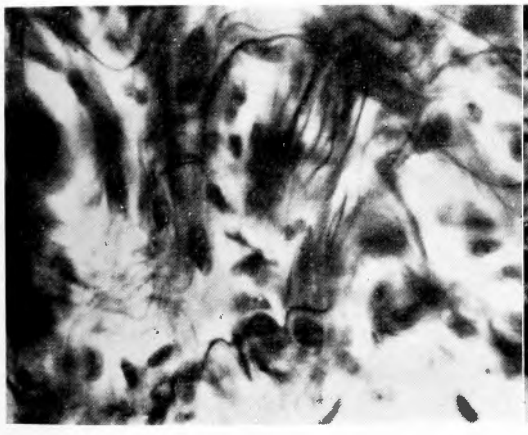

Fig. 27

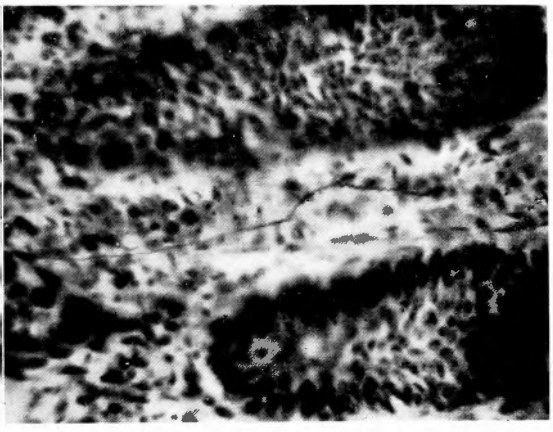

Fig. 28

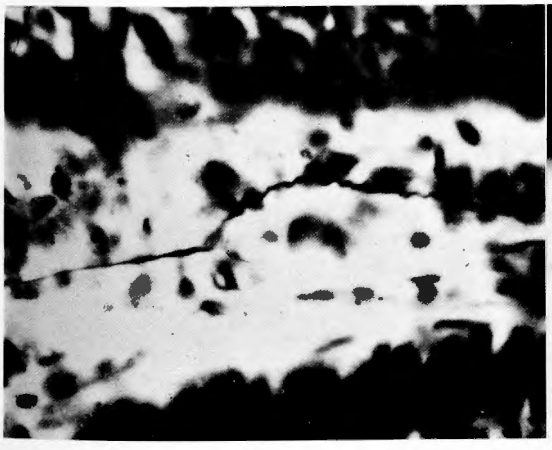

Fig. 29

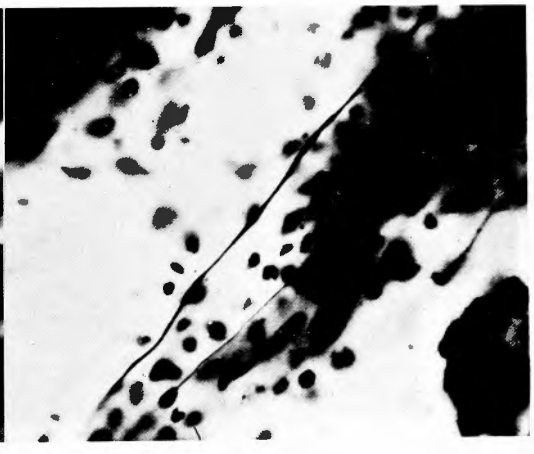

Fig. 30

Fig 31

Fig. 32

Fig. 33

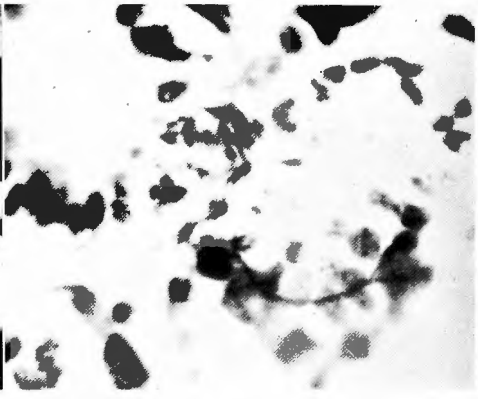

Fig. 34

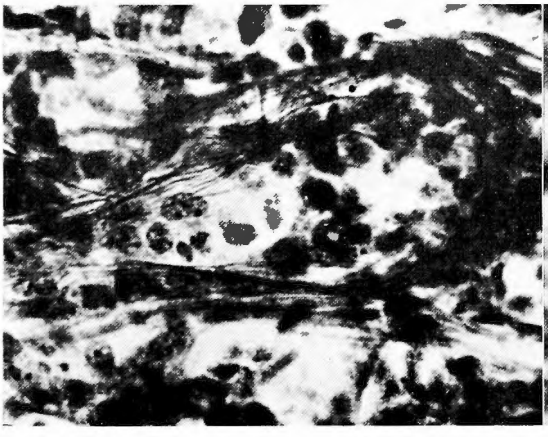

Fig. 35

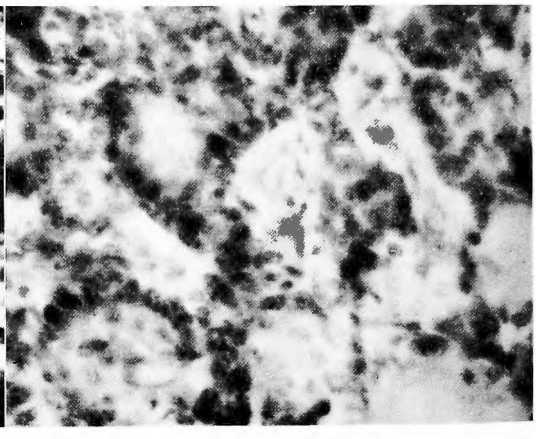

Fig. 36